REMARKS

Claims 1-20, 23 and 25-30 were pending in the subject application. By this Amendment applicants have amended claims 1, 6, 11-13, 16, 23, 29 and 30, and added new claims 31-37. Accordingly, claims 1-20, 23 and 25-37 are pending in the subject application.

Abstract

On page 2 of the November 19, 2001 Office Action, the Examiner objected to the Abstract on the ground that it does not appear on a separate sheet.

In response, applicants, attach as Exhibit A the Abstract of the Invention on a separate sheet, and have above requested its entry.

Rejection under 35 U.S.C. § 112, first paragraph

On page 2 of the November 19, 2001 Office Action, the Examiner rejected claim 30 under 35 U.S.C. § 112, first paragraph.

In response, without conceding the correctness of the Examiner's position, applicants have amended claim 30 to clarify the informalities the Examiner referred to.

Rejection under 35 U.S.C. § 112, second paragraph

On pages 2-4 of the November 19, 2001 Office Action, the Examiner rejected claims 11-13, 16 and 29 under 35 U.S.C. § 112, second paragraph.

In response, applicants have amended claims 11-13, 16 and 29 to clarify the informalities the Examiner referred to.

Rejections under 35 U.S.C. § 102 and § 103

On pages 4-5 of the November 19, 2001 Office Action, the Examiner rejected claims 1, 3, 6, 9, 11, 14-20 and 30 under 35 U.S.C. § 102 as allegedly anticipated by U.S. Patent No. 5,206,021 ("the '021 patent").

On pages 6-7 of the November 19, 2001 Office Action, the Examiner rejected claims 1-9, 11-20, 25-27 and 30 under 35 U.S.C. § 103 as allegedly unpatentable over the '021 patent.

In response, applicants initially point out that the rejections based on the '021 patent should not be asserted for the first time in a final Office Action. While the Examiner stated that applicants' amendments necessitated these new grounds of rejection, applicants respectfully disagree. Applicants' September 20, 2001 Amendment merely corrected informalities in the claims. The September 20, 2001 Amendment in no way altered the scope of the claims so as make the '021 patent for the first time relevant to the claims after amendment. Thus, to the extent the '021 patent is relevant to the currently pending claims, it was also relevant to the claims prior to the September 20, 2001 Amendment.

Accordingly, if the §102 and § 103 rejections based on the '021 patent are not withdrawn, applicants respectfully request that the finality of the November 19, 2001 Office Action be withdrawn pursuant to M.P.E.P. § 706.07(d).

Turning to the substance of the rejections, applicants point out that the '021 patent fails to teach topical compositions having enhanced transdermal permeation characteristics of pharmacologically active agents. Each of the underlined terms clearly distinguishes the claimed invention from the '021 patent,

which is only concerned with pesticide formulations that are toxic to any subject with a dermis. Moreover, applicants have amended claim 1 to recite pharmacologically active agent that are "desirable for transdermal permeation". Pesticides are not desirable for transdermal permeations.

the '021 patent is directed to oil-in-water emulsions for application to crops (see column 15, line 22) for the control of pests (see column 15, line 19). As the Examiner indicates, the oil-in-water emulsion may contain, in the oil phase, a mixture of lipophilic substances, the mixture exhibiting a eutectic point, whose eutectic point is either below 100°C or in the range -20°C to +30°C. Applicants' claims, as amended, require that the composition be pharmacologicaly desirable and pharmaceutically acceptable, as well as, the requirement that the composition be suitable "for mutual enhancement of transdermal permeation of at least a first and a second pharmaceutically acceptable components which are both pharmacologically active agents".

First of all, pesticides are not pharmaceutically acceptable and pharmacologically active agents. In this regard, attention is drawn to page 2, lines 21 and 22 of the present specification, which refers to drugs as being synonymous with pharmacologically active agents. Pesticides are not drugs. Pesticides are applied topically to plants and also to materials such as cloths. Pesticides are generally considered as not being pharmaceutically acceptable for transdermal permeation/absorption. It is generally accepted by those skilled in the art that a major concern for all pesticides is their potential for toxicity to a human or other animal following transdermal permeation and subsequent distribution into the systemic circulation of the human or other animal body. Indeed, it is believed that the

"Gulf War Syndrome" may relate to adverse reactions to pesticides which had been applied to tents and their subsequent transdermal absorption. For these reasons, a skilled reader would not dismiss the relevance of the '021 patent, which concerns itself solely with pesticides, from a consideration of topical, pharmacologically desirable, pharmaceutically acceptable compositions.

As already mentioned, it is not desirable that pesticides be suitable for transdermal permeation. For this reason, we have qualified the term "pharmacologically active agents" by the expression "that are desirable for transdermal permeation". In addition, a skilled reader would appreciate that the '021 patent is silent on whether its compositions are suitable for mutual enhancement of transdermal permeation of each active agent. Instead, the skilled reader would be inclined to believe and, indeed hope, that pesticides would not show enhanced permeation, of even a single active agent, into the crop being protected. Furthermore, there is nothing in the '021 patent to suggest that its compositions would show mutually enhanced permeation into crops which its compositions were applied.

The Examiner has suggested that certain anti-fungal and anti-bacterial agents are disclosed at column 9 and 10 of the '021 patent. Of the various lipophilic pesticidal substances disclosed at columns 9 and 10, binapacryl, dicofol and nitrofen are banned, under EU Directive 79/117/EEC, from even being placed on the market, even for application in a specified manner, because their use can give rise to harmful effects on human health or the environment. In addition, azinphos ethyl, DNOC, monolinuron and pyrazophos are not authorised for use, even as pesticides, under EU Directive 91/414/EEC. Furthermore, aldicarb is treated as a poison under the Poisons Law! The inclusion of

such pesticidal substances in the lists disclosed at columns 9 and 10 would dissuade a skilled reader from actively considering whether two or more of these substances might be suitable for incorporation in a topical, pharmacologically desirable, pharmaceutically acceptable composition for transdermal permeation.

The Examiner goes on to draw attention to column 10, lines 27-29, of the '021 patent suggesting that an organic solvent may be used but is not necessary. It is, however, important to emphasise that, in this sentence, the word "dissolved" is used. This suggest to the skilled reader that, in those emulsions, the lipophilic pesticidal substance, or mixture, is either in solid form or, less likely, is in the form of a eutectic mixture which eutectic mixture, even if formed, which we deny, is dissolved or broken down, by the solvent. In that latter eventuality, no eutectic mixture would be present in the topical composition itself. We respectfully suggest that the Examiner's conclusion that the subject-matter of claim 9 lacks novelty is erroneous. The Examiner goes on to suggest that, if an organic solvent is used, the subject-matter of claims 3 and 6 also lacks novelty. For the same reason, the Examiner's conclusion is, we contend, erroneous.

Column 10 of the '021 patent, at lines 35-44, teaches various solvents, for dissolving the lipophilic pesticidal substance(s). Specifically disclosed are kerosenes and chlorinated solvents such as carbon tetrachloride and chloroform. These solvents are not suitable for application to at least human skin and would not be considered as pharmacologically desirable and pharmacuetically acceptable. Once again, their inclusion in a list of suitable solvents would dissuade a skilled reader from actively considering whether the teaching of the '021 patent is any

relevance to topical, pharmacologically desirable, pharmaceutically acceptable compositions.

Column 12 of the '021 patent, at lines 47, 59, teaches various surfactants for incorporation in the compositions. Specifically disclosed are various mercaptans and thio compounds which would not be considered as pharmacologically desirable and pharmaceutically acceptable. Once again, their inclusion in a list of suitable surfactants would dissuade a skilled reader form actively considering the '021 patent in relation to topical, pharmacologically desirable, pharmaceutically acceptable compositions.

Accordingly, the '021 patent does not anticipate applicants' claims, as amended. Furthermore, as discussed below, the '021 patent does not make applicants' claims obvious.

The relevant art to the subject matter claimed is the art of transdermally delivering pharmacologically active agents. Firstly, one skilled in the art would not turn to the field of pesticides for any such insight. It seems self-evident that pesticides are intended to kill pests on a surface, by contact with that surface. It is further self-evident that it is not at all desirable that pesticides be able to permeate the surface since, in that case, ingestion of the crops could lead to toxicity issues. For these reasons, nothing in the '021 patent could be construed to suggest permeation, by even a single active agent and, still further, nothing in the '021 patent suggests mutual enhancement of permeation of two or more pharmacologically active agents.

Furthermore, the international Examiner had already considered the relevance of -a copy of the IPER is available to the Examiner

becuase this application is a §371 of the PCT International Application in which the IPEP was issued. In paragraph 2.4 of the IPER, the international Examiner, noted as a point that the present independent claims refer to topical compositions for mutual enhancement of transdermal permeation. The international Examiner concluded that it was clear that compositions containing pesticides, i.e. substances which are virtually toxic to humans, are not topical compositions suitable for transdermal permeation within the meaning of the present application. To this end, attention is drawn to the definition of the term "pharmacological agent" which appears at page 6 of the description as originally filed, namely, that the term means any agent used in the prophylaxis or therapy of any condition affecting the health of the human or animal species. Pesticides do not fall within such definition.

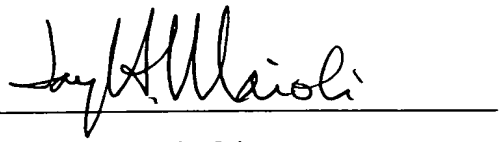
Applicants also draw the Examiner's attention to the secondary considerations which are supportive of a finding of non-obviousness. Specifically, the inventors overcame a technical prejudice in the art which conventionally considered, at the time the invention was made, that the formation of eutectic mixtures is undesirable, as discussed at page 2, lines 3-19 of the specification. In addition, the at least two pharmacologically active agents of the eutectic mixture of the discontinuous phase support each other in their effects so that a new technical result is achieved. Specifically, mutual enhancement of transdermal permeation of each of the first and second pharmacologically active agents was observed and was exemplified and this could not have been predicted from the known properties of each of the individual active agents. We would submit that this is a surprising synergistic effect, which is clearly exemplified in the examples and corresponding figures.

Accordingly, applicants respectfully request withdrawal of the §§ 102 and 103 rejections, or withdrawal of the finality of the November 19, 2001 Office Action.

In view of the foregoing amendments to the specification and claims, applicants respectfully request reconsideration and withdrawal of the rejections and objections set forth in the November 19, 2001 Office Action.

No fee, other than the enclosed $920.00 extension of time fee, is deemed necessary in connection with the filing of this Response. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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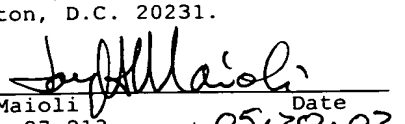

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Date 05.20.02

ATTACHMENT A
CLAIMS AS AMENDED WITH MARKINGS TO SHOW CHANGES
SERIAL NO. 09/423,715

1. (Amended) A topical pharmacologically desirable, pharmaceutically acceptable composition for mutual enhancement of transdermal permeation of at least a first and a second pharmaceutically acceptable components which are both pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase comprising a "eutectic mixture of first and second pharmacologically active agents" that are desirable for transdermal permeation" and the continuous phase comprising a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the provisos that when the ~~at least~~ first ~~and second~~ pharmacologically active agent~~s~~ is a local anesthetic, the second pharmacologically active agent is not a ~~are each not~~ local anaesthetic~~s~~ or, when the second pharmacologicaly active agent is a local anesthetic, the first pharmacologically active agent is not a local anesthetic.

2. The topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, and the second pharmacologically active agent has a melting point between -40°C and 150°C.

3. The topical composition according to Claim 1, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.

4. The topical composition according to Claim 3, in which the third pharmaceutically acceptable component has a melting point between 40 and 150°C.

5. The topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.

6. (Amended) The topical composition according to Claim ~~1~~ 3, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.

7. The topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C.

8. The topical composition according to Claim 6 or 7, in which the fourth component comprises a fourth pharmacologically active agent.

9. The topical composition according to Claim 1, in which said at least one discontinuous phase contains no co-solvent or additional oil phase, so that the ~~eutectic mixture~~ substantially comprises the or each discontinuous phase of the emulsion.

10. The topical composition according to Claim 1, in which the first pharmacologically active agent is selected from the group consisting of triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine, sulfiram, oxybutynin, capsaicin, testosterone enanthate and choline salicylate.

11. (Amended) The topical composition according to Claim 1, in which the second pharmacologically active agent is selected from the group consisting of non-steroid anti-inflammatory arylpropionic agents, ~~acid derivatives, aryl acetic acid derivatives, arylcarboxylic acids,~~ narcotic analgesics, anti-fungal agents, antibacterial agents, anticholinergics, anthelmintics, antihistaminics, and antihypertensives.

12. (Amended) The topical composition according to Claim 8, in which the third and fourth pharmacologically active agents are each selected from the group consisting of non-steroid anti-inflammatory agents, ~~arylpropionic acid derivatives, aryl acetic acid derivatives,~~ narcotic analgesics, anti-fungal agents, antibacterial agents, anticholinergics, antihypertensives, antihistaminics, and anthelmintics.

13. (Amended) The topical composition according to Claim 3 or 4, in which the third pharmaceutically acceptable component is ~~selected from~~ lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.

14. The topical composition according to Claim 1, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier containing substantially water as the continuous phase.

15. The topical composition according to Claim 1, in which the pharmaceutically acceptable carrier contains at least one gelling or suspension agent.

16. (Amended) The topical composition according to Claim 15, in which the gelling or suspension agent is selected from the group consisting of carbomers, modified celluloses

~~derivatives~~, naturally-occurring synthetic or semi-synthetic gums, modified starches, co-polymers formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylates ~~derivatives~~ or a mixture thereof.

17. The topical composition according to Claim 1, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or soft gelatin capsule.

18. The topical composition according to Claim 1, in which the emulsifying agent is selected from the group consisting of non-ionic, cationic and anionic surfactants.

19. The topical composition according to Claim 18, in which the emulsifying agent is a non-ionic surfactant.

20. The topical composition according to Claim 1, in which the at least two pharmacologically active agents are structurally and/or pharmacologically diverse.

23. (Amended) A method for mutual enhancement of dermal permeation of at least a first and a second pharmaceutically acceptable components which are both pharmacologically active agents, the method comprising applying a topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase comprising a eutectic mixture of first and second pharmacologically active agents and the continuous phase

comprising a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the provisos that ~~the at least first and second pharmacologically active agents are each not local anaesthetics,~~ , when the first pharmacologically active agent is a local anesthetic, the second pharmacologically agent is not a local anesthetic, or, when the second pharmacologically active agent is a local anesthetic, the first pharmacologically acitve agent is not a local anesthetic, to an accessible body surface of an animal.

25. The topical composition according to claim 2, wherein the first pharmacologically active agent has a melting point between 40 and 50°C, and the second pharmacologically active agent has a melting point between -5 and 90°C.

26. The topical composition according to claim 4, wherein the third pharmaceutically acceptable component has a melting point between 40 and 75°C.

27. The topical composition according to claim 7, wherein the fourth pharmaceutically acceptable component has a melting point between 40 and 75°C.

28. The topical composition according to claim 11, wherein the second pharmacologically active agent is selected from the group consisting of triclosan, chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate, ibuprofen, ketoprofen, fenoprofen, flurbiprofen, etodolac, fentanyl, econazole, ketoconazole, mupirocin, chlorbutanol, clindamycin, iodine, oxybutynin, tetramisole, triprolidine, promethazine, and propranolol.

29. (Amended) The topical composition according to Claim 12, wherein the third and fourth pharmacologically active agents are each selected from the group consisting of triclosan, chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate, ibuprofen, ketoprofen, fenoprofen, flurbiprofen, etodolac, ~~arylcarboxylic acids,~~ fentanyl, econazole, ketoconazole, mupirocin, chlorbutanol, clindamycin, iodine, oxybutynin, propranolol, triprolidine, promethazine, and tetramisole.

30. (Amended) The topical composition according to Claim 16, wherein the gelling or suspension agent is selected from the group consisting of xanthan gum, acacia, tragacanth, ~~maleic anhydride copolymers, methyl vinyl ether,~~ and a mixture thereof.

31. (New) The topical composition according to Claim 9, in which said at least one discontinuous phase contains no co-solvent or additional oil phase, so that the eutectic mixture essentially consists of the or each discontinuous phase of the emulsion.

32. (New) The topical composition according to Claim 14, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier essentially consisting of water as the continuous phase.

33. (New) The method of claim 23, wherein the animal is a human.

34. (New) The method according to Claim 23, in which said at least one discontinuous phase contains no co-solvent or additional oil phase, so that the eutectic mixture

substantially comprises the or each discontinuous phase of the emulsion.

35. (New) The method according to Claim 34, in which said at least one discontinuous phase contains no co-solvent or additional oil phase, so that the eutectic mixture essentially consist of the or each discontinuous phase of the emulsion.

36. (New) The method according to Claim 23, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier containing substantially water as the continuous phase.

37. (New) The method according to Claim 36, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier essentially consisting of water as the continuous phase.

EXHIBIT A

Abstract of the Invention

The invention concerns a topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmaceutically acceptable components which are both pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40 °C. The topical composition may additionally comprise, in the eutectic mixture, a third or fourth pharmaceutically acceptable component.